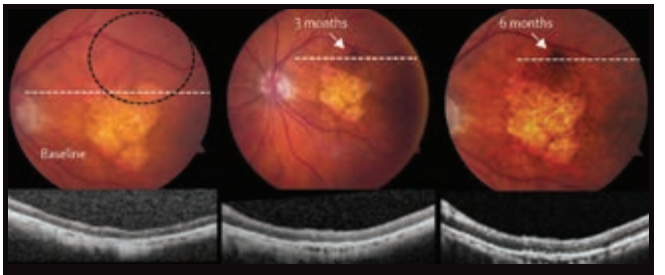
Stem Cell Studies Show Safety & More



STEM CELL PROGRESS. Fundus photos taken at baseline and at three and six months in a patient with AMD show pigmented patch of transplanted hESC RPE cells that becomes larger and more pigmented over time. Dotted circle indicates transplanted area. OCTs show these cells on Bruch's membrane at the same time points.

Interim analysis of two ongoing phase 1/2 trials of human embryonic stem cell (hESC) grafting into the subretinal space provides the first human use data on the medium- to long-term safety, graft survival, and biological activity of tissue derived from pluripotent stem cells.[1]

One trial included nine patients with atrophic age-related macular degeneration (dry AMD) and the other, nine patients with Stargardt macular dystrophy. Each patient received a transplant, in the worse eye, of hESC-derived retinal pigment epithelium placed between the compromised central macular tissue and fairly normal peripheral tissue. At baseline, all patients had very limited vision due to advanced disease.

Treatment appears safe. After 37 months, none of the concerns commonly raised about use of hESCs—tumor formation, immune reactions, or cell differentiation into unwanted cell types—materialized in these trials, and no serious safety events related to the transplanted cells occurred.

Of the 18 total patients in both groups, 13 showed favorable increases in subretinal pigmentation, the area of which increased in density and size over time.

Surprise visual benefits. Though no improvement was expected in the phase 1 patients, visual acuity and function were tested as part of the safety evaluation. Surprisingly, more than half of the treated eyes—but none of the untreated eyes—showed improved vision. Eight patients' visual acuity increased by at least 15 letters within one year of surgery. Participants also noted improvement in their general vision, near and distance activities, and peripheral vision as measured with the National Eye Institute Visual Function Questionnaire 25 subscales.

"We need to take these results with a grain of salt," said coauthor Carl D. Regillo, MD, "as it's very difficult to accurately assess visual function in patients who have such limited vision. Still, evidence of any improvement is encouraging." Dr. Regillo is leading the trials at Wills Eye Hospital, where he is director of the retina service.

Looking ahead. "We used four different cell doses in the phase 1 trials," he said. "In phase 2 we'll push the dose a bit higher and implant cells in eyes with less advanced disease in hopes of seeing a more definitive favorable visual effect."

At the time of transplant, hESC-derived RPE cells are somewhat immature, and Dr. Regillo noted that

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their potential ability to mature within the retina may offer vital advantages. For instance, the tissue may be less immunogenic and more likely to survive and function than mature tissue. There may be other benefits, as well: Cell differentiation can be controlled to ensure optimum tissue safety and functionality before transplantation; cell lines can be tested to eliminate disease-associated genetic abnormalities; and since hESC proliferate continuously, they offer a virtually unlimited supply of "starter" cells.

Positive RPE trial safety results bolster the hope that hESC could be used in other diseased tissues, for example, to regenerate heart cells after myocardial infarction, replace islet cell in patients with diabetes, or replace neural cells in ischemic stroke, Parkinson disease, or Alzheimer disease.

—Mary Wade

1 Schwartz SD et al. *Lancet.* Published online Oct.15, 2014. doi:10.1016/S0140-6736(14)61376-3.

Dr. Regillo receives research funding from Ocata Therapeutics.

Bevacizumab vs. Ranibizumab

Meta-analysis May Quell Systemic Safety Concerns

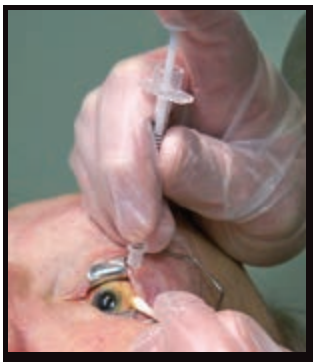
A new Cochrane Review of major clinical trials on the relative safety of bevacizumab (Avastin) and ranibizumab (Lucentis) concluded that the systemic safety of the two drugs appears to be similar in patients with neovascular age-related macular degeneration (AMD).[1]

Some interpretations of safety findings from the earlier CATT (Comparison of AMD Treatment Trials) and IVAN (Inhibit VEGF in Age-related Choroidal Neovascularisation) studies had raised concerns that bevacizumab might elevate the risk of serious adverse events. Accordingly, certain national health systems set policies limiting the use of bevacizumab, and some ophthalmologists followed suit. Given the price difference between bevacizumab and ranibizumab, such policies came at a steep price.

Reconsidering the concerns. The new Cochrane Review may put to rest some of those safety concerns. "Our study concludes that policies that require the use of ranibizumab to treat neovascular AMD for reasons of systemic safety are not sustained by the evidence," said Koren H. Kwag, MSc, a lead author, at the Clinical Epidemiology Unit, IRCCS Galeazzi Orthopaedic Institute, Milan, Italy.

"When we compared all serious systemic adverse events (SSAEs), and when we compared SSAEs by organ system class or by specific adverse events, we found no significant differences between the drugs, with the exception of gastrointestinal disorders."

Study details. This meta-analysis, conducted by a multinational research team, synthesized the results of nine randomized controlled trials that compared the drugs head to head. The trials selected for inclusion comprised 3,665 participants who received either bevacizumab or ranibizumab for up to two years. All studies used the approved dosage of ranibizumab (0.5 mg) or the most common bevacizumab dosage for AMD (1.25 mg), though the dosing regimen—monthly or as needed—varied among the studies. None of the trials received funding from the manufacturer.



WHICH DRUG TO USE? Bevacizumab and ranibizumab have similar systemic safety, says recent meta-analysis.

Safety statistics. Two primary outcomes were studied: all-cause mortality and all SSAEs. Based on the results of eight studies (n = 3,338), the estimated risk ratio (RR) of death with bevacizumab compared with ranibizumab was 1.10 (95 percent confidence interval [CI], 0.78-1.57, p = .59) at maximum follow-up of one or two years. This gives a 3.4 percent risk of death with ranibizumab and a 3.7 percent risk with bevacizumab (CI, 2.7-5.3 percent).

For all SSAEs (nine studies, n = 3,665), the estimated RR was 1.08 for bevacizumab versus ranibizumab (CI, 0.90-1.31, p = .41). This gives a risk of SSAEs of 22.2 percent with ranibizumab and 24 percent with bevacizumab (CI, 20.0-29.1 percent).

Secondary analysis showed that the only significant difference in systemic safety between the drugs was an increased risk of gastrointestinal disorders for patients treated with bevacizumab. The difference was small (1.3 percent higher with bevacizumab) and not attributable to any specific gastrointestinal disorder.

Limitations. The authors rated the quality of the evidence as "low to moderate" due to study limitations such as heterogeneity between study populations and dosing regimens. Although no significant safety differences were detected between the drugs, the study could not definitely rule out the possibility that either treatment is less harmful than the other. Finally, they said that the conclusions should be verified once the unpublished results of three of the included studies are available.

—Mary Wade

1 Moja L et al. *Cochrane Database Syst Rev.* 2014(9). doi:10.1002/14651858.CD011230.pub2.

Dr. Kwag reports no related financial interests.

NATALIE LOYACANO, COMT, ROUB, OSA, OCS

Oculoplastic Advances

3-D Printer Creates Orbital Prosthesis

PROSTHESIS FROM A PRINTER. (ABOVE) This patient, who underwent exenteration, is wearing a prosthesis on her right side. (LEFT) A closer look at the 3-D printed prosthesis.

In his quest for a low-cost prosthesis to minimize the "devastating psychological trauma" of facing the world with an empty orbital socket, David T. Tse, MD, FACS, turned to 3-D printing. This novel technology has been used to fabricate everything from jewelry to astronaut tools. Dr. Tse and a team at the University of Miami's Composite Materials Lab have harnessed it to make an orbital prosthesis that is less expensive and more easily obtained than conventionally fabricated models.

How 3-D printing works. A mobile scanner captures images of both the empty socket and the eye and eyelids on the undamaged side. Computer software then creates a mirror image of the normal side to fit over the empty socket. Finally, the computer directs a 3-D printer to "print" the actual prosthesis by building up successive layers of polymer, suffused with a nanoclay, that match the patient's skin tone and iris color.

Advantages. 3-D printing has several advantages over the conventional fabrication process, said Dr. Tse, at Bascom Palmer Eye Institute, where he is a professor of ophthalmology and the Nasser Ibrahim Al-Rashid Chair in Ophthalmic Plastic, Orbital Surgery, and Oncology. The process reduces costs substantially, from $15,000 to $500, and it's fast. It captures an individual's unique coloration and orbital defect geometry for optimal match and fit. And the digital scans can be acquired remotely, enabling access in places where skilled ocularists are rare.

The process is being fine-tuned, but the goal is to soon offer prostheses to patients anywhere in the world, Dr. Tse said. "The exenterated socket and the normal eye can be scanned remotely, and the data downloaded in Miami for fabrication. The 3-D–printed prosthesis can be mailed to the patient the next day."

—Miriam Karmel

Dr. Tse reports no related financial interests.

Vitreoretinal Findings

Vitrectomy Linked With Sustained IOP Elevation

Pars plana vitrectomy for epiretinal membrane (ERM) appears to increase the risk of sustained elevated intraocular pressure (IOP), particularly in the setting of pseudophakia or a family history of glaucoma, a retrospective study has concluded.[1]

Lead author Lihteh Wu, MD, and coauthors from the Pan American Collaborative Retina Study Group retrospectively examined IOP data from 198 patients who had a vitrectomy and membrane peeling for idiopathic macular ERM. Average follow-up was 47.3 ± 24 months (range, 12-106 months). Dr. Wu is a vitreoretinal surgeon at the Instituto de Cirugia Ocular in San José, Costa Rica.

Results. Sustained IOP elevation was defined as IOP of 24 mmHg or greater or an increase of 5 mmHg or more that persisted for two visits and warranted IOP-lowering therapy. It developed in 38 vitrectomized eyes (19.2 percent) compared with nine (4.5 percent) of the unoperated fellow eyes ($p < .0001$), the researchers found. The only statistically significant IOP risk factors in the vitrectomized eyes were cataract surgery ($p < .0270$) and a family history of open-angle glaucoma ($p < .0004$).

Clinical implications. "Comprehensive ophthalmologists should be aware that patients who have undergone a vitrectomy, even if it's uncomplicated, may develop ocular hypertension over the long term. So they should keep checking the pressure regularly, particularly if the patient has undergone cataract surgery," said Dr. Wu.

In addition, he advised cataract surgeons to watch for elevated IOP over several months in patients who had a previous vitrectomy. "This is a problem that develops slowly over time," he said.

The group is now conducting a prospective study to confirm the findings.

—Linda Roach

1 Wu L et al. *Retina*. 2014; 34(10):1985-1989.

Dr. Wu reports no related financial interests.